



Docket No.: 273802002200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jacob Sten PETERSEN

Application No.: 09/064,682

Group Art Unit: 1645

Filed: April 22, 1998

Examiner: R. Swartz

For: COMBINATIONS OF ANTIGEN AND
MUCOSAL BINDING COMPONENTS FOR
INDUCING SPECIFIC IMMUNOLOGICAL
TOLERANCE

**DECLARATION OF JAN HOLMGREN
PURSUANT TO 37 C.F.R. § 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Jan Holmgren, hereby declare as follows:

1. I am Professor and Head of the Department of medical microbiology and immunology at Göteborg University, Sweden, and also Director of the Göteborg University Vaccine Research Institute. I have published almost 500 papers in the fields of microbiology, immunology and vaccinology and have been an elected member of various societies and academics including the Swedish Royal Academy of Science and the Royal Academy of Engineering. I currently belong to the Board of Directors of the Knut and Alice Wallenberg Foundation (Sweden) and the International Vaccine Institute (IVI) and also am a member of various vaccine-related technical task forces or steering committees for the Global Alliance for Vaccines and Immunisation (GAVI), the DOMI program of IVI, and the World Health Organization (WHO). Other details of my credentials are listed in my curriculum vitae, which is attached as Exhibit 1.

2. Dr. Jacob Sten Petersen, inventor of the above-mentioned patent application, has shown me the patent application and the Office Action mailed January 14, 2003 in the above-identified application and has asked if I, in my capacity as an expert in the field of mucosal immunology and oral-mucosal tolerance, could write a brief opinion about the main criticisms brought forward in the Office Action, which I am pleased to do here.

3. In the Office Action, the Examiner argues that the invention made in the patent application is not sufficiently novel or unexpected based mainly on two published documents used singly or in combination: Elson: Curr Top Microbiology 1999, 146:29033 and Tsuru: Japan patent JP 03109328. I do not agree with the Examiner's analysis, since I find the invention to be both novel and unexpected and I cannot find anything in the two cited documents or elsewhere that either singly or in combination could have predicted the invention even to an expert in the field.

4. Elson and others before him teach that cholera toxin B subunit (CTB) is by itself a strong mucosal immunogen and may also serve as an adjuvant for admixed, mucosally co-administered antigens in *stimulating* mucosal and peripheral-systemic immune responses. There is nothing to teach that mucosally administered CTB could instead, or alternatively, induce peripheral-systemic tolerance for selected co-administered admixed antigens as taught by Petersen in the patent application. Instead it was taught by Sun et al PNAS 1994, 91:10795-99 that mucosally administered CTB can induce such tolerance *only when conjugated with* selected antigens, which further supports the notion that the claimed invention by Dr. Petersen is both novel and unexpected.

5. Likewise, there is nothing in the document by Tsuru, that either taken alone or in combination with Elson or other material known at the time for the patent application invention, could have predicted the invention. Tsuru teaches that pretreatment with CTB can be used, *preferably by a non-mucosal route*, to facilitate better survival of transplanted tissue but any such effect has nothing to do with the mucosal induction of peripheral-systemic tolerance to a co-administered antigen such as insulin but is rather an unspecific killing effect of high doses of CTB on lymphocytes, where it has been described that the main effector cells for graft rejections, CD8+ CTLs, are especially sensitive to this nonspecific cytotoxic action of high doses of CTB. The document can in no way guide or predict the invention claimed in the patent application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: _____
Jan Holmgren